Pharmacology of pulmonary vasodilators

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Last updated 28/10/2022 - 17:46

This chapter is related to the aims of Section F11(iii) from the 2017 CICM Primary Syllabus, which expects the exam-going trainees to be able to *"outline the pharmacology of drugs used to treat acute pulmonary hypertension"*. This chapter on the pharmacology of pulmonary vasodilators is separated from nitric oxide for no specific reason, other than the author's desire to cover that gas in some detail, compared to the lack of such desire for other pulmonary vasodilators. To be fair, Question 14 from first paper of 2011 and Question 17 from the second paper of 2020 were the only Part One questions which asked about this topic, and they were both quite iNO-centric. Moreover in Question 4 from the first paper of 2022, the college examiners complained that iNO was covered rather poorly in the candidates' answers (only 15% passed this question). The other pulmonary vasodilator which can be given in the inhaled manner are nebulised prostacycline and, to a lesser extent, oxygen. Beyond the CICM question, the syllabus does not specify that only "inhaled" vasodilators will be asked about, and so this chapter also needs to cover some of the non-inhaled substances. Though of course that distinction is quite artificial, because just about anything can be inhaled even though it might not be ordinarily meant for inhalational use.

These substances will be covered here in some bare minimum of detail. Contrary to popular belief among the senior members of college faculties, rote learning facts about drugs is not conducive to the understanding of their function or to understanding the principles of their safe responsible use. However, some remembered facts were apparently expected by the examines in Question 14. In short, *"accurate detail concerning the receptor and second messenger effects of drugs was expected. The importance of V/Q matching and reduction in systemic effects via inhalational administration needed to be stated. Better answers included discussion of serious adverse effects"*. For the best single reference, it is difficult to go past "Pulmonary vasodilators" by Mark S. Siobal (2007), but realistically even this single article may be excessive.

In briefest summary:

Inhaled Pulmonary Vasodilators		
Name	**Nitric oxide**	**Epoprostenol**

Class	Inhaled pulmonary vasodilator	Inhaled pulmonary vasodilator
Chemistry	A free radical with the formula NO	Synthetic analogue of the naturally occurring eicosanoid prostacyclin (prostaglandin I2 or PGI2)
Routes of administration	Administered as part of inspired gas mixture, usually as an admixture fraction measured in tens of ppm, via a proprietary system (INOMax)	Can be intravenous, but usually nebulised as a part of a solution with a glycine buffer, using a continuous ultrasonic nebuliser
Absorption	Absorbs rapidly into the pulmonary circulation via the lungs	Absorbs rapidly into the pulmonary circulation via the lungs
Solubility	As it dissociates in water, nitric oxide produces nitric acid (HNO3) which has a pKa of -1.3	Natural pKa is 4.4; requires a diluent which contains glycine and sodium hydroxide. The pH of the reconstituted drug mixture has a pH of around 12, because the drug tends to spontaneously hydrolyse in aqueous solution at a normal pH
Distribution	VOD is impossible to measure, but is potentially very large. NO reacts with oxygen and water to produce nitrogen dioxide and nitrites, which then bind to haemoglobin and produce either nitrosylhaemoglobin or methaemoglobin, i.e. it can be described as "highly protein bound".	0.357L/kg
Target receptor	Soluble guanylyl cyclase (which is induced by NO)	Activates G protein-coupled PGE receptors on platelets and endothelial cells, which activates adenlyl cyclase and increases cAMP
Mechanism of action	Inhibits vasoconstriction by increasing the amount of cyclic GMP (cGMP) in the cytosol, thus decreasing the amount of cytosolic calcium ions available to sustain smooth muscle contraction	Increased cyclic AMP leads to decreased platelet activation and activates PKA, which phosphorylates and inhibits myosin light-chain kinase which leads to smooth muscle relaxation and vasodilation
Metabolism	One way or another, nitric oxide ends up as methaemoglobin and nitrate. Either it reacts with lung	Degrades spontaneously as well as enzymatically into about sixteen major and minor metabolites

	water, becoming nitrite (which reacts with oxyhemoglobin and generates methaemoglobin and nitrate) or it combines directly with oxyhaemoglobin, with the same results. If it encounters hypoxic blood, it can combine with deoxyhaemoglobin to create nitrosyl-haemoglobin, which then rapidly becomes methaemoglobin when it contacts oxygen.	
Elimination	Nitrates are eliminated mainly in urine whereas methaemoglobin is metabolised in several hours into haemoglobin by endogenic reductases. The nitrates excreted in urine represent over 70% of the inhaled NO dose.	Half-life is about six minutes
Time course of action	Onset of effect is seen within seconds	Platelet inhibition effects last up to 2 hrs; smooth muscle vasodilation is very shortlived (comparable with half-life)
Clinical effects	Apart from pulmonary vasodilation, there is methemoglobinaemia, hypotension (maybe some of it does leak into the systemic circulation, or maybe this the effect of depressed LV function, rebound hypoxia after abrupt withdrawal, thrombocytopenia (in as many as 10% of patients) and increased susceptibility to pulmonary infections probably due to NO2 formation and associated lung injury.	Vasodilation (pulmonary as well as systemic); inhibition of platelet aggregation; facial flushing, tachycardia, bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying
Single best reference for further information	TGA (AusPAR) product information	Flolan PI by GlaxoSmithCline

In addition to this, the college examiners complained in their comments to Question 14 from first paper of 2011 that "many candidates neglected to include oxygen which is also a drug with significant pulmonary vasodilating properties." Fine, here's a table of its pharmacological properties. However, it must be pointed out that it *prevents or reverses vasoconstriction*, i.e it does not have a very potent vasodilator function for patients whose oxygenation is normal. Of course that's quite a pointless comment to make, considering one would never be giving oxygen to those people. In the hypoxic population, restoring normal oxygenation can halve pulmonary vascular resistance, according to Roberts et al (2001).

Name	**Oxygen**
Class	Vital ingredient of multicellular life
Chemistry	Diatomic gas
Routes of administration	Inhaled; also as intravenous or intra-arterial infusion of well-oxygenated blood (i.e. ECMO), and can be given externally (as in hyperbaric oxygen therapy)
Absorption	Absorbs rapidly into the pulmonary circulation via the lungs (250ml/min with 21% FiO2, at rest)
Solubility	Poor solubility in water
Distribution	Widely distributed- total body oxygen content is 64% by weight. Highly protein-bound (to haemoglobin)
Target receptor	Cytochrome c mitochondrial enzymes
Mechanism of action	Increases ATP by acting a substrate for aerobic metabolism of glucose
Metabolism	Metabolised in all tissues (mainly brain, heart and skeletal muscle) Mainly metabolised by cytochrome c mitochondrial enzymes (90%) Zero-order clearance kinetics, roughly 200ml/minute
Elimination	Rapidly eliminated by metabolism into CO2 and water
Time course of action	Minutes
Clinical effects	Drying of mucous membranes and inspissation of secretions Inflammatory tracheobronchitis Decreased central respiratory drive (minimally) Hypecapnoea in "CO2 retainers" mainly by virtue of V/Q mismatch and Haldane effect Absorption atelectasis

	Increased left-to-right shunting in ASDs Increased peripheral vascular resistance Cerebral and coronary vasoconstriction Euphoria Retrolental fibroplasia of the newborn Decreased erythropoiesis
Single best reference for further information	Haim Bitterman's 2009 article, "Bench-to-bedside review: oxygen as a drug"

Other pulmonary vasodilators

Non-inhaled pulmonary vasodilators also exist, and they can be broadly separated into two groups: phosphodiesterase inhibitors and endothelin receptor antagonists.

A Comparison of Phosphodiesterase Inhibitors			
Name	Sildenafil	Tadalafil	Milrinone
Class	Pulmonary vasodilator	Pulmonary vasodilator	Ino-dilator
Chemistry	Pyrazolopyrimidine	Pyrazinopyridoindole	Biperidine
Routes of administration	Oral, but also available as an attractive buccal spray	Oral	IV; but can also be administed as a nebulised aerosol, and had initially been marked as an oral preparation
Absorption	Rapidly absorbed after oral administration, with a mean absolute bioavailability of 41%; a high-fat meal reduces absorption	Appears to have a high oral bioavailability	Well absorbed orally; 92% oral bioavailability
Solubility	Basic drug, with a pKa value of 8.7; highly (96%) protein-bound	Acidic drug, pKa ~ 3.5; highly protein bound (94%)	pKa 4.6 and 8.5; good solublity at physiological pH

Distribution	Very large VOD: 105 L/kg; i.e extensively distrbuted into tissues	very large VOD: 64 L/kg	0.38L/kg; 70% protein bound
Target receptor	Phosphodiesterase 5	Phosphodiesterase 5	Phosphodiesterase 3
Mechanism of action	Increases cyclic GMP by inhibiting phosphodiesterase 5, which is responsible for cGMP catabolism. Selective for vascular smooth muscle.	Increases cyclic GMP by inhibiting phosphodiesterase 5, which is responsible for cGMP catabolism. Selective for vascular smooth muscle.	Increases cyclic AMP by inhibiting phosphodiesterase 3, which is responsible for cAMP catabolism. Selective for vascular smooth muscle and cardiac muscle.
Metabolism	Cleared predominantly by the liver: metablised by CYP3A into an active metabolite which itself has about 50% of th PDE5-inhibiting potency of the parent drug	Hepatic clearance is the main mode; metabolised by CYP 3A4 into a totally inactive metabolite	Mostly cleared renally; of the free fraction some undergoes hepatic metabolism into an inactive o-glucouronide, and the rest is excreted unchanged at a rate which varies depending on renal blood flow
Elimination	Half life of sildenafil and its major metabolite is about 4 hours.	Half-life is 17.5 hrs	Half life is 2.3 hours in patients with heart failure, slightly less in normal healthy adults and longer in patients with renal dysfunction
Time course of action	Vasodilation is maximal approximately 1-2 hours after dosing	Effects are maximal ~ 2 hours following oral administration	Onset of action is usually within 5-15 minutes
Clinical effects	Pulmonary vasodilation, systemic vasodilation with hypotension, reflex tachycardia in reponse to this; priapism; headache	Pulmonary vasodilation, systemic vasodilation with hypotension, reflex tachycardia in reponse to this; priapism; headache	Improved vntricular contractility; decreased systemic vascular resistance; decreased pulmonary vascular resistance; tachycardia; propensity to arrhythmias.

Single best reference for further information	REVATIO product pamphlet (sildenafil citrate)		Canadian (Novopharm) product pamphlet for milrinone lactate

For completeness, the following table contains details about the two most popular endothelin-1 receptor antagonists. There is no possible way this could ever be viewed as core material even by the most deranged examiners. The only halfway interesting thing to remember about these drugs is the fact that, unlike the vast majority of drugs, they are excreted almost exclusively via the bile.

Name	**Bosentan**	**Ambrisentan**
Class	Pulmonary vasodilator	Pulmonary vasodilator
Chemistry	Pyrimidine derivative	Propionic acid
Routes of administration	Oral	Oral
Absorption	50% oral bioavailability	90% oral bioavailability
Solubility	pKa 5.8; highly protein-bound (98%);	99% protein bound; this drug is a carboxylic acid with a pKa of 4
Distribution	Large VOD, 28L/kg	Large VOD, 40L/kg
Target receptor	Endothelin receptor types ETA and ETB	Endothelin receptor types ETA and ETB
Mechanism of action	Bosentan is a non-selective ETA and ETB receptor antagonist. By competitive inhbition, bosentan prevents binding of endothelin to its ETA receptor, which would usually produce smooth muscle contraction (vasoconstriction). ETA are G-protein coupled receptors; activating them leads to an increase in cAMP and an increased availability of intracellular calcium which gives rise to vasoconstriction.	Ambrisentan is a selective ETA receptor antagonist. By competitive inhbition, ambrisentan prevents binding of endothelin to its ETA receptor, which would usually produce smooth muscle contraction (vasoconstriction). ETA are G-protein coupled receptors; activating them leads to an increase in cAMP and an increased availability of intracellular calcium which gives rise to vasoconstriction.

Metabolism	Hepatic metabolism and almost completely biliary elimination; only 3% of the dose is recovered from the urine. Only of the metabolites is effective and probably contributes 10-20% of the total drug effect	Ambrisentan is excreted largely unchanged (45.6% of the dose); excretion is biliary. The rest is glucouronidated and oxidised by CYP3A4 into relatively inactive metabolites
Elimination	Terminal elimination half-life is about 5 hours in healthy adult subjects	In humans, the terminal half-life following oral administration was determined to be approximately 15 hours
Time course of action	Effects are maximal ~ 1 hour following oral administration	Maximum plasma concentrations (Cmax) of ambrisentan typically occur around 1.5 hours post dose
Clinical effects	Pulmonary vasodilation, fluid retention, pulmonary veno-occlusive disease, foetal toxicity, anaemia	Pulmonary vasodilation, fluid retention, pulmonary veno-occlusive disease, foetal toxicity, anaemia, LFT derangedment ("transaminitis"),
Single best reference for further information	FDA information on the TRACLEER brand of bosentan	TGA information pamphlet for the VOLIBRIS brand of ambrisentan

Previous chapter: Pharmacology of nitric oxide

Next chapter: Pharmacology of drugs used to treat asthma

References

Roberts, David H., et al. "Oxygen therapy improves cardiac index and pulmonary vascular resistance in patients with pulmonary hypertension." *Chest* 120.5 (2001): 1547-1555.

Siobal, Mark S. "Pulmonary vasodilators." *Respiratory care* 52.7 (2007): 885-899.

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